STIC-ILL

5/2645

From: Gambel, Phillip
Sent: Friday, September 24, 2004 6:09 PM
To: STIC-ILL
Subject: tnf and hepatitis 10 /043,436

NPL ___ Adonis ___
MIC ___ BioTech X MAIN ___
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Ck Cite ___ Dupl Request ___
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stic

please provide the following references to

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----------tnf and hepatitis 10 /043,436 ----------

7/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0013535860 BIOSIS NO.: 200200129371
Clinical and cytokine response to anti-TNF antibody therapy in severe alcoholic hepatitis
AUTHOR: Jalan Rajiv (Reprint); Williams Roger; Kaser Arthur; Davies Nathan A; Zoller Heinz; Hodges Stephen J; Graziadei Ivo; Shawcross Deborah; Vogel Wolfgang; Alisa Akeel; Ludwiczek Othmar; Tilg Herbert
AUTHOR ADDRESS: University College London, London, UK**UK
JOURNAL: Hepatology 34 (4 Pt. 2): p441A October, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 52nd Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 09-13, 2001; 20011109
ISSN: 0270-9139
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

----------tnf and hepatitis 10 /043,436 ----------

COMPLETED

09462123 PMID: 1401067
Degradation of endogenous bacterial cell wall polymers by the muralytic enzyme mutanolysin prevents hepatobiliary injury in genetically susceptible rats with experimental intestinal bacterial overgrowth.
Lichtman S N; Okoruwa E E; Keku J; Schwab J H; Sartor R B
Department of Pediatrics, University of North Carolina, Chapel Hill 27599-7220.
Journal of clinical investigation (UNITED STATES) Oct 1992, 90 (4) p1313-22, ISSN 0021-9738 Journal Code: 7802877
Contract/Grant No.: AR-39480; AR; NIAMS; DK-34987; DK; NIDDK; DK-40249; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Jejunal self-filling blind loops with subsequent small bowel bacterial overgrowth (SBBO) induce hepatobiliary injury in genetically susceptible Lewis rats. Lesions consist of portal tract inflammation, bile duct proliferation, and destruction. To determine the pathogenesis of SBBO-induced hepatobiliary injury, we treated Lewis rats with SBBO by using several agents with different mechanisms of activity. Buffer treatment, ursodeoxycholic acid, prednisone, methotrexate, and cyclosporin A failed to prevent SBBO-induced injury as demonstrated by increased plasma aspartate

1075

LIVER FIBROSIS IS DRAMATICALLY REDUCED IN CARBON TETRACHLORIDE INJURED JUND GENE KNOCKOUT MICE. Derek A Mann, David E Smart, University of Southampton, Southampton Uk; Jonathan B Weitzman, Institue Pasteur, Paris France; Moshe Yaniv, Institute Pasteur, Paris France; Michael J Arthur, University of Southampton, Southampton Uk

Purpose: The activation of hepatic stellate cells (HSC) to a myofibroblast-like phenotype is the central event in hepatic wound healing and fibrosis. Recent work in our laboratory has focused on the role of the AP-1 (Jun and Fos) transcription factor as a regulator of HSC activation (1,2). Jun protooncogenes (c-Jun, JunB and JunD) are key components of the dimeric transcription factor AP-1 and act as regulators of many cell functions characteristic of the activated phenotype of HSC (e.g. proliferation, apoptosis, matrix synthesis and turnover, expression of cytokines etc). In vitro and in vivo studies from our laboratory have shown that JunD expression is induced during HSC activation and is the predominant Jun family protein expressed in these cells (1,2). We have recently described how JunD is required for high level activity of the tissue inhibitor of metalloproteinases-1 (TIMP-1) and interleukin-6 (IL-6) gene promoters in activated rat HSC (2). These data prompted us to explore the possibility that JunD can function as a transcription regulator of liver fibrogenesis. JunD gene knockout mice have recently been described and other than defects in spermatogenesis are apparently normal (3). Methods: Adult male JunD knockout and wild type control mice were given an intraperitoneal injection of a 1:4 mix of CCl4: olive oil (25 microlitres CCl4/100g body weight) twice weekly over a period of 8 weeks to induce chronic liver injury. Liver sections from culled mice were then analysed histochemically for the extent of fibrosis and collagen deposition. Results and Conclusions. The results showed that JunD knockout mice displayed a dramatically attenuated phenotype, with a substantially reduced level of fibrosis relative to that observed in wild type mice. Reduced levels of collagen deposition and numbers of activated HSC relative to these parameters in controls was observed in all JunD knockout mice. We conclude that JunD is a regulator of the expression of profibrogenic genes in activated HSC and plays a critical role in the fibrogenic process in vivo. JunD should therefore now be considered as an important target for drug design. 1Bahr MJ et al (1999) Hepatology 29, 839-848 2Smart DE et al (2001) J. Biol. Chem (In press) 3Thepot D et al (2000) Development 127, 143-153

1076

A GENETIC MUTATION IN THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR ALPHA GENE IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS. Raphael B Merriman, Bradley E Aouizerat, Mary J Molloy, John P Kane, University of California, San Francisco, San Francisco, CA; Bruce Bacon, St Louis University, St. Louis, MO; Nathan M Bass, University of California, San Francisco, San Francisco, CA

Introduction: Non-alcoholic steatohepatitis (NASH) is characterized by elevated transaminases, with steatosis and necroinflammatory changes on liver biopsy, in patients without significant alcohol ingestion. The pathogenesis is poorly understood but likely to include genetic and environmental factors that affect lipid homeostasis. Lipid abnormalities are common in patients with NASH. Peroxisome Proliferator-Activated Receptor alpha (PPARα) is a member of the steroid hormone receptor superfamily and a ligand-activated transcription factor. PPARα mediates the hypolipidemic effects of fibrates in the treatment of hypertriglyceridemia. PPARα is a major and integral regulator of intra- and extracellular lipid utilization and is highly expressed in tissues with a high rate of fatty acid oxidation especially liver, heart and kidney. Consequently, a minor alteration in PPARα function could have a pronounced effect particularly in pathologic conditions such as diabetes or insulin resistance. Recently, a functional missense mutation (C to G transversion) of the PPARα gene, changing leucine to valine at nucleotide 482 in exon 5 (L162V) in the DNA binding domain, has been described. This mutation has been associated with both altered lipid profiles and transcriptional activity in vitro. The potential relevance of the L162V mutation in PPARα in patients with NASH is unexplored. Aim: To determine the prevalence of a recently described significant mutation (L162V) in the PPARα gene in patients with NASH. Methods: Sixty-four patients with previously well-defined NASH, for whom liver biopsy material was available, were evaluated. DNA was isolated from archival formalin-fixed paraffin-embedded liver biopsy specimens using standard techniques. PCR amplification of exon 5 was performed with described intronic primers and the PCR products analyzed for single base changes using optimized denaturing gel gradient electrophoresis. Results: Exon 5 was successfully amplified in 40 of 64 patient samples. Six L162V heterozygote mutations in exon 5 of PPARα were detected in the 40 samples, representing a heterozygote frequency in this NASH population of 15%. The expected frequency of this mutation in PPARα is 4%, based upon a previously well-defined control population of 360 patients. The increased incidence of this mutation in patients with NASH is highly significant, even for this limited-size population ($0.01 > p > 0.005$, chi-squared test with Yates correction factor). Conclusions: The prevalence of a recently described functional heterozygote mutation in the PPARα gene (L162V) is significantly increased in a population of patients with well-defined NASH. This finding requires verification in a larger patient group and determination of its functional significance in terms of lipid and lipoprotein metabolism, hepatic pathophysiology and therapeutic implications in patients with NASH.

1077

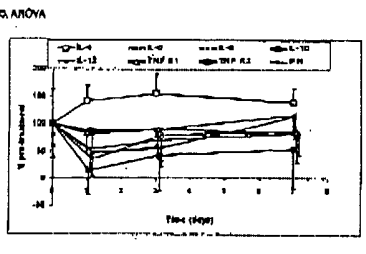
CLINICAL AND CYTOKINE RESPONSE TO ANTI-TNF ANTIBODY THERAPY IN SEVERE ALCOHOLIC HEPATITIS. Rajiv Jalan Dr, University College London, London United Kingdom; Roger Williams Prof, University College Hospital, London United Kingdom; Arthur Kaser Dr, University Hospital, Innsbruck Austria; Nathan A Davies Dr, University College London, London United Kingdom; Heinz Zoller Dr, University Hospital, Innsbruck Austria; Stephen J Hodges Dr, University College London, London United Kingdom; Ivo Graziadei Dr, University Hospital, Innsbruck Austria; Deborah Shawcross Dr, University College London, London United Kingdom; Wolfgang Vogel Dr, University Hospital, Innsbruck Austria; Akeel Alisa Dr, Cromwell Hospital, London United Kingdom; Othmar Ludwiczek Dr, Herbert Tilg Prof, University Hospital, Innsbruck Austria

Hypothesis and Aims. Severe alcoholic hepatitis (AH) is associated with high mortality and tumour necrosis factor-alpha (TNFα) has been implicated in the aetiology of this disease. This study was designed to test the hypothesis that administration of the anti-TNF monoclonal antibody to patients with AH would improve their outcome by altering the pro and anti-inflammatory cytokine balance. The aims of this study were to evaluate the safety, efficacy and cytokine response to intravenous administration of anti-TNF antibody (infliximab, 5mg/Kg) in patients with severe AH. Methods. 12 patients (5Iyrs, 35-67; all males, Maddrey discriminant factor>32) with biopsy confirmed AH were included. Exclusions:bleeding, untreated infection, hepatorenal syndrome, HIV/HCV, pregnancy,malignancy, severe co-morbid disease. Serial measurements were made for plasma cytokine levels using ELISA assays, specifically; IL-1β; IL-4; IL-6; IL-8; IL-10; IL-12; TNFα; IFNγ; IL-1RA; TNF-R1; and TNF-R2. Results. Ten of the twelve patients are alive at a median of 7.5 (1-14) months. Two patients died within 30 days from uncontrolled sepsis. Bilirubin levels and Maddrey score reduced significantly (Table 1). Serial cytokine data are summarised in the Figure. The overall trend suggests an early decrease in inflammatory mediators (IL-6, IL-8, IFNγ). The change in IL-8 levels is of particular interest due to its accepted role in neutrophil recruitment. IL-1β and TNFα were near the detection limits of the assays making interpretation difficult. IL-4, which has been suggested to act as a stimulus for TH2 lymphocyte recruitment, was found to increase and remain elevated. Whereas IL-10, a reputed anti-inflammatory cytokine, was decreased following treatment. The soluble TNF receptors R1 and R2, did not change. Conclusions. Anti-TNF was well tolerated and the increased survival suggests that this treatment is effective in AH. The post anti-TNF survival rate in these patients of 83% is encouraging when compared to the expected 3-month mortality rate of over 70% (using MELD/Maddrey). The cytokine results indicate that there is an early anti-inflammatory response to the treatment, and that there may be a longer-term effect on lymphocyte recruitment. This latter effect being mediated by IL-4, through a shift to a TH2 population of T-helper lymphocytes. The results provide a possible pathophysiological basis for the observed clinical response. The positive findings of this pilot study justifies a randomised clinical trial and extended mechanistic studies.

Changes in Bilirubin and Maddrey Score following anti-TNF antibody

	Day 0	Day 7	Day 14	Day 28
Bilirubin	307 (147-582)	331 (82-841)	278 (44-606)	184 (29-248)*
Maddrey	57 (38-121)	60 (23-109)	46 (36-87)	48 (17-70)*

*p<0.05, ANOVA



1078

CD8⁺ T LYMPHOCYTE MEDIATED BYSTANDER HEPATITIS IN A TRANSGENIC MOUSE MODEL. David G Bowen, Alessandra Warren, AW Morrow Gastroenterology and Liver Ctr, Cent Institute, Camperdown NSW Australia; Barbara Fazekas de St Groth, Centenary Institute, Camperdown NSW Australia; Geoffrey W McCaughan, Patrick Bertolino, AW Morrow Gastroenterology and Liver Ctr, Cent Institute, Camperdown NSW Australia

Intrahepatic accumulation of CD8⁺ T cells following antigen-specific activation has been demonstrated in a number of transgenic models, and also by tetramer labelling in extra-hepatic viral infections. In some transgenic models, intrahepatic accumulation of cytotoxic T lymphocytes (CTL) is associated with hepatitis. This observation has led to the proposal that hepatocellular damage may occur in some forms of autoimmune hepatitis on the basis of a "bystander injury", whereby CTL accumulating in the liver mediate injury to non-antigen bearing hepatocytes in a non-specific manner. It has also been speculated that this mechanism may contribute to immune mediated hepatocellular damage associated with chronic HCV infection, as CTL derived from chronically HCV infected individuals may mediate injury to non-antigen bearing target cells *in vitro*. In order to investigate whether bystander damage to non-antigen bearing hepatocytes occurs *in vivo*, we have developed a transgenic mouse model in which the antigen is not expressed by hepatocytes, but limited to bone marrow derived antigen presenting cells (APCs). Methods: Two lines of transgenic mice were utilised. In the first, Des mice, all CD8⁺ T cells express a transgenic T cell receptor specific for the mouse class I antigen $H\text{-}2K^b$ associated with an unknown self peptide. The second transgenic line, 178.3, expresses the $H\text{-}2K^b$ molecule ubiquitously under the control of its own promoter. Bone marrow (BM) chimeric mice were also generated, in which syngeneic, non-transgenic B10.BR mice were reconstituted with 178.3 BM following lethal irradiation. In these mice, only BM derived APCs express $H\text{-}2K^b$; hepatocyte expression was excluded by immunohistochemistry and flow cytometric analysis. The experiments comprising this study involved adoptive transfer of T cells from Des mice into both intact 178.3 mice and 178.3 BM→B10.BR chimeras. Results: Despite the ubiquitous expression of the specific antigen in 178.3 mice, adoptively transferred CD8⁺ Des T cells rapidly and preferentially accumulated within the liver. Subsequently, a transient hepatitis occurred, peaking at day 2, and resolving by day 3-4. Transfer of Des T cells into 178.3 BM→B10.BR chimeras also resulted in rapid intrahepatic accumulation of CD8⁺ Des T cells , followed by hepatitis with similar tempo to that observed in intact 178.3 mice. The hepatitis occurring in 178.3 BM→B10.BR chimeras was a bystander effect, with hepatocyte damage secondary to immune activation mediated by professional APCs. The occurrence of hepatitis in this model was not ablated by the depletion of NKT cells, the administration of blocking anti INF-γ antibodies, or the elimination of Fas expression on hepatocytes via creation of 178.3 BM→lpr chimeras. Discussion: Despite ubiquitous expression of the specific antigen in the 178.3 model, autoreactive CD8⁺ T cells accumulated preferentially within the liver, leading to the rapid onset of hepatitis. Antigen expression by hepatocytes was not required for either this rapid accumulation or the subsequent hepatitis, since similar results were obtained using 178.3 BM→B10.BR chimeras. Hepatocellular damage was not ablated by various manoeuvres blocking single cytotoxic pathways; the mechanisms underlying such bystander damage to hepatocytes remain to be delineated, however, may well constitute a complex interplay of such mediators. To our knowledge, this is the first demonstration that bystander hepatitis can occur *in vivo* following antigen-specific CD8⁺ T cell activation. Such mechanisms may play a role in some forms of biologically significant hepatitis, including autoimmune hepatitis associated with extra-hepatic autoimmune disease.

Gambel, Phillip

From: Gambel, Phillip
Sent: Friday, September 24, 2004 6:09 PM
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Subject: tnf and hepatitis 10 /043,436

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----------tnf and hepatitis 10 /043,436 ----------

7/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013535860 BIOSIS NO.: 200200129371
Clinical and cytokine response to anti-TNF antibody therapy in severe alcoholic hepatitis
AUTHOR: Jalan Rajiv (Reprint); Williams Roger; Kaser Arthur; Davies Nathan A; Zoller Heinz; Hodges Stephen J; Graziadei Ivo; Shawcross Deborah; Vogel Wolfgang; Alisa Akeel; Ludwiczek Othmar; Tilg Herbert
AUTHOR ADDRESS: University College London, London, UK**UK
JOURNAL: Hepatology 34 (4 Pt. 2): p441A October, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 52nd Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Dallas, Texas, USA November 09-13, 2001; 20011109
ISSN: 0270-9139
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

----------tnf and hepatitis 10 /043,436 ----------

09462123 PMID: 1401067
Degradation of endogenous bacterial cell wall polymers by the muralytic enzyme mutanolysin prevents hepatobiliary injury in genetically susceptible rats with experimental intestinal bacterial overgrowth.
Lichtman S N; Okoruwa E E; Keku J; Schwab J H; Sartor R B
Department of Pediatrics, University of North Carolina, Chapel Hill 27599-7220.
Journal of clinical investigation (UNITED STATES) Oct 1992, 90 (4) p1313-22, ISSN 0021-9738 Journal Code: 7802877
Contract/Grant No.: AR-39480; AR; NIAMS; DK-34987; DK; NIDDK; DK-40249; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Jejunal self-filling blind loops with subsequent small bowel bacterial

overgrowth (SBBO) induce hepatobiliary injury in genetically susceptible Lewis rats. Lesions consist of portal tract inflammation, bile duct proliferation, and destruction. To determine the pathogenesis of SBBO-induced hepatobiliary injury, we treated Lewis rats with SBBO by using several agents with different mechanisms of activity. Buffer treatment, ursodeoxycholic acid, prednisone, methotrexate, and cyclosporin A failed to prevent SBBO-induced injury as demonstrated by increased plasma aspartate aminotransferase (AST) and elevated histology scores. However, hepatic injury was prevented by mutanolysin, a muralytic enzyme whose only known activity is to split the beta 1-4 N-acetylmuramyl-N-acetylglucosamine linkage of peptidoglycan-polysaccharide (PG-PS), a bacterial cell wall polymer with potent inflammatory and immunoregulatory properties. Mutanolysin therapy started on the day blind loops were surgically created and continued for 8 wk significantly diminished AST (101 +/- 37 U/liter) and liver histology scores (2.2 +/- 2.7) compared to buffer-treated rats (228 +/- 146 U/liter, $P < 0.05$, 8.2 +/- 1.9, $P < 0.001$ respectively). Mutanolysin treatment started during the early phase of hepatic injury, 16-21 d after surgery, decreased AST in 7 of 11 rats from 142 +/- 80 to 103 +/- 24 U/liter contrasted to increased AST in 9 of 11 buffer-treated rats from 108 +/- 52 to 247 +/- 142 U/liter, $P < 0.05$. Mutanolysin did not change total bacterial numbers within the loop, eliminate Bacteroides sp., have in vitro antibiotic effects, or diminish mucosal PG-PS transport. However, mutanolysin treatment prevented elevation of plasma anti-PG antibodies and tumor necrosis factor-alpha (TNF alpha) levels which occurred in buffer treated rats with SBBO and decreased TNF alpha production in isolated Kupffer cells stimulated in vitro with PG-PS. Based on the preventive and therapeutic activity of this highly specific muralytic enzyme, we conclude that systemic uptake of PG-PS derived from endogenous enteric bacteria contributes to hepatobiliary injury induced by SBBO in susceptible rat strains.
Record Date Created: 19921113
Record Date Completed: 19921113

----------tnf and hepatitis 10 /043,436 ----------

/7/23 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11344813 PMID: 11433695
Acute alcoholic hepatitis: treatments]
Hepatite alcoolique aigue: ses traitements.
Naveau S
Service d'Hepato-Gastroenterologie, Hopital Antoine Beclere, 157, rue de la Porte de Trivaux, F 92141 Clamart. sylvie.naveau@abc.ap-hop-paris.fr
Presse medicale (Paris, France - 1983) (France) Jun 9 2001, 30 (20) p1024-30, ISSN 0755-4982 Journal Code: 8302490
Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: FRENCH
Main Citation Owner: NLM
Record type: Completed
PROGNOSIS: Acute alcoholic hepatitis (AAH) is a severe form of alcohol-related liver disease with a high short-term mortality that can reach 50%. Long-term outcome depends on definitive weaning from alcohol and the development of cirrhosis. ESSENTIAL THERAPEUTIC STEP: Abstention from alcohol is the number one therapeutic measure required for treating AAH. Abstention must be total and definitive. THERAPEUTIC STRATEGIES: The pathogenic mechanisms involved in AAH have led to close assessment of numerous treatment protocols. Thirty-three randomized trials have evaluated drug treatments based on various strategies: antiinflammatory action using corticosteroids or colchicine; reduction of the hypermetabolism using

propylthiouracil; hepatoprotective effect against oxidative stress using cyanidanol, alpha lipoid acid, silymarine, amlopidine, malotilate; vasodilatation to improve oxygenation of the centrolublular region using a calcium channel inhibitor, amlopidine; increased liver regeneration using anabolism steroids, intravenous perfusion combining insulin and glucagon; antifibrosis action using colchicine, D penicillamine; improved microcirculation due to increased deformability of the red cells and inhibition of TNF-alpha using pentoxifyllin. Eleven therapeutic trials have investigated the effect of parenteral or enteral artificial nutrition. GOLD STANDARD TREATMENT: Among all these strategies, the only one with a proven efficacy is corticosteroid therapy. Four trials have demonstrated the effect of corticosteroid therapy on short-term survival and 3 of the 4 meta-analyses devoted to the topic have demonstrated the usefulness of corticosteroid therapy in severe forms defined by a Maddrey index > or = 32: bilirubin in mumol per liter/17 + 4.6 (patient's PT in seconds--control PT in seconds) and the presence or not of encephalopathy. The gold standard treatment for severe AAH is oral prednisolone 40 mg/d for 1 month (excluding contraindications). PERSPECTIVES: Despite the effect of corticosteroid therapy, mortality at 2 months in severe AAH is still about 30%. Recent experimental data suggest that monoclonal anti-TNF alpha antibodies could be useful. (73 Refs.)
Record Date Created: 20010703

----------tnf and hepatitis 10 /043,436 ----------

14027527 PMID: 9727645
Tumor necrosis factor and alcoholic liver disease.
McClain C J; Barve S; Barve S; Deaciuc I; Hill D B
Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, Lexington 40536-0084, USA.
Alcoholism, clinical and experimental research (UNITED STATES) Aug 1998 , 22 (5 Suppl) p248S-252S, ISSN 0145-6008 Journal Code: 7707242
Contract/Grant No.: 1K20 AA00190-01; AA; NIAAA; 1K21 AA00205-01; AA; NIAAA; 1P01 NS31220-01A1; NS; NINDS; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Increased levels of hepatic and serum tumor necrosis factor (TNF) have been documented in animal models of alcoholic liver disease and in human alcoholic liver disease. This dysregulated TNF metabolism has been postulated to play a role in many of the metabolic complications and the liver injury of alcoholic liver disease. One potential therapy for alcoholic liver disease may be agents that downregulate TNF production or block TNF activity. Indeed, agents such as prostaglandins and glucocorticoids (both inhibit TNF production) have been used in both human liver disease and experimental models of liver injury, and anti-TNF antibody has recently been shown to attenuate the hepatotoxicity in an animal model of alcoholic-related liver disease. In this study, we demonstrate that a simple ex vivo system can be used to initially assess potential efficacy of anticytokine agents when administered to humans. Both prednisone and a prostaglandin analog were effective in downregulating TNF and interleukin-8 production. The liver is normally resistant to TNF cytotoxicity. Sensitivity to TNF cytotoxicity is thought to occur when there is inadequate production of hepatic protective factors. In this study, we showed that, when patients with acute alcoholic hepatitis were matched with trauma patients for serum levels of interleukin-6, they had similar depressions in the negative acute phase protein, albumin, but markedly different increases in the major acute phase protein, C reactive protein. Patients with alcoholic hepatitis had a very blunted response. We also showed that inhibiting activation of the redox sensitive transcription factor NFkappaB sensitizes to TNF-induced hepatocyte death in vitro. This

transcription factor is important for the production of both cytokines and many acute phase protective factors. Several hepatic protective factors are induced by TNF. One possible mechanism for liver injury in alcoholic hepatitis may be inadequate generation of hepatic protective factors. Our future understanding of mechanisms of alcoholic liver disease will involve understanding the balance between noxious and protective factors in the liver, and this should lead to rational therapy for this disease process.
Record Date Created: 19981216
Record Date Completed: 19981216

----------tnf and hepatitis 10 /043,436 ----------

7/7/20 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

07658445 EMBASE No: 1999138232
Tumour necrosis factor antagonists
Chantry D.
D. Chantry, ICOS Corporation, 22021 20th Avenue S.E., Bothell, WA 98021 United States
AUTHOR EMAIL: dchantry@icos.com
Emerging Drugs (EMERG. DRUGS) (United Kingdom) 1999, 4/- (5-13)
CODEN: EMDRF ISSN: 1361-9195
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 31

Tumour necrosis factor (TNF) has been shown to play a pivotal role in immune and inflammatory responses. Inappropriate or over-expression of TNF is a hallmark of a number of diseases including rheumatoid arthritis (RA), Crohn's disease and sepsis. Inhibition of TNF production has been shown to be beneficial in a wide range of preclinical models of inflammatory disease making inhibition of TNF production or signalling an appealing target for the development of novel anti-inflammatory drugs. Initial efforts in this area have focused on the use of TNF binding proteins (monoclonal antibodies to TNF and soluble derivatives of the two TNF receptors) as therapeutic agents. This review will outline the data supporting a role for TNF as a mediator of inflammation and will subsequently focus on the recent clinical experience with TNF inhibitors in Crohn's disease and RA.

----------tnf and hepatitis 10 /043,436 ----------

7/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0008727429 BIOSIS NO.: 199395029695
Beneficial effects of post-transfusional hepatitis in acute myelogenous leukemia may be mediated by lipopolysaccharides, tumor necrosis factor alpha and interferon-gamma
AUTHOR: Treon S P; Broitman S A (Reprint)
AUTHOR ADDRESS: Dep. Microbiol., Boston Univ. Sch. Med., Boston, Mass. 02118, USA**USA
JOURNAL: Leukemia (Basingstoke) 6 (10): p1036-1042 1992
ISSN: 0887-6924
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Post-transfusional hepatitis is often a complication in patients with acute myelogenous leukemia (AML) in whom survival is paradoxically prolonged. The etiology is unknown. In previous studies, we showed that impaired hepatic endotoxin (lipopolysaccharide, LPS) clearance in patients with acute viral hepatitis A, B, or C versus controls results in endotoxemia and tumor necrosis factor-alpha (TNF-alpha) release. TNF-alpha mediates anti-proliferative and differentiating effects in AML cell lines. Interferon-gamma (IFN-gamma) released in acute viral hepatitis, acts in synergy with TNF-alpha. HL60, KG1, and U937 AML cells treated 3, 6, and 9 days with physiologically attainable TNF-alpha (10 U/ml), IFN-gamma (100 U/ml) and LPS (10 ng/ml) levels have significantly diminished viability and cell growth versus controls. Treatment of HL60 AML cells with LPS/TNF-alpha/IFN-gamma also resulted in significantly increased monocytic pathway differentiation not seen with KG1 or U937 AML cells. HL60 AML cells treated with TNF-alpha/IFH-gamma for 6 days released endogenous TNF-alpha (1.57 U/10-6 cells) upon LPS stimulation compared to lt 0.012 U/10-6 cells in non-LPS-stimulated TNF-alpha/IFN-gamma-treated cells or untreated cells (p lt 0.0001). Untreated HL60 AML cells co-cultured with HL60 cells pretreated for 6 days with TNF-alpha/IFN-gamma and then subjected to LPA stimulation had significantly diminished cell growth compared to control (p lt 0.0001). This effect could be reversed with anti-TNF-alpha- antibody, supporting the concept that endogenous TNF-alpha release by LPS/ TNF-alpha/IFN-gamma treated HL60 AML cells may act by paracrine means to supports growth of other AML cells. The beneficial effects of posttransfusional hepatitis in AML patients may be mediated via LPS/TNF-alpha-IFN-gamma-induced AML cell growth suppression and/or terminal differentiation in which AML cells participate by releasing TNF-alpha after being actid upon LPsTGN-alpha/IFN-gamma. Endogenously released TNf-alpha might then act by autocrine/paracrine means to mediate further suppression and terminal differentiation.